Eur J Clin Microbiol Infect Dis (2010) 29:59–62
DOI 10.1007/s10096-009-0820-7

ARTICLE

Hantavirus nephropathy as a pseudo-import pathology from Ecuador

R. Demeester · E. Bottieau · M. Van Esbroeck · M. R. Pourkarim · P. Maes · J. Clement

Received: 24 August 2009 / Accepted: 15 September 2009 / Published online: 11 October 2009

Abstract We report a case of hantavirus infection (nephropathia epidemica) diagnosed in a Belgian backpacker returning from a trekking expedition in Ecuador, after likely heavy exposure to rodents. Because of epidemiological inconsistency, molecular investigation was performed and revealed a *Puumala* infection acquired during very limited exposure in Belgium upon return.

Introduction

Clinical presentations of hantavirus infections are classically divided into two main syndromes depending on the etiological serotypes: hemorrhagic fever with renal syndrome (HFRS), including a milder form called nephropathia epidemica (NE), and hantavirus pulmonary syndrome (HPS). HFRS is predominantly observed in Europe and Asia and is mainly due to the *Puumala* or *Dobrava* and the *Hantaan* or *Seoul* virus respectively, while HPS has been exclusively reported in the Americas and may be caused by numerous serotypes (*Sin Nombre*-like viruses) [1]. *Seoul* virus (SEOV) is the only hantavirus found worldwide because its rodent host, the wild rat (*Rattus rattus* and *R. norvegicus*) is ubiquitous [2]. However, to our knowledge, no cases of hantavirus nephropathy have been reported in Ecuador to date.

R. Demeester (✉)
University Hospital Saint-Pierre,
Department of Internal Medicine,
Rue Haute, 322,
1000 Brussels, Belgium
e-mail: rdemeest@ulb.ac.be

R. Demeester · E. Bottieau · M. Van Esbroeck
Department of Clinical Sciences, Institute of Tropical Medicine,
Antwerp, Belgium

M. R. Pourkarim · P. Maes · J. Clement
Hantavirus Reference Centre, Laboratory of Clinical Virology,
Rega Institute for Medical Research, University of Leuven,
Leuven, Belgium

Case report

We report the case of a 22-year-old woman, living in Antwerp city (Belgium), who developed in September 2007 severe generalized muscle aching 11 days after returning from a 23-day expedition in Ecuador. She had traveled throughout the country as a backpacker and had visited at the end of her trip the Amazonian region, where she spent several days in primitive conditions (sleeping in huts, bathing in rivers). She had been previously vaccinated against hepatitis A and B and typhoid fever and had been taking atovaquone-proguanil properly as malaria prevention. Her symptoms started (day 0) with an abrupt high fever (40°C), followed by abdominal pain and backache (day 1 post-onset of symptoms [POS]), and vomiting and diarrhea (day 2 POS). The patient was seen on the same day by a general practitioner who prescribed antipyretics. At day 5 POS, she was admitted to the University Hospital of Antwerp. Her temperature was 38.4°C, blood pressure 120/90 mmHg, and oxygen saturation was 100%; both kidney regions were sensitive and there was a discrete rash on the legs. Laboratory findings at admission (day 5 POS) revealed a lowered platelet count and elevated levels of liver transaminases, lactate dehydrogenase, and C-reactive protein (Table 1). The level of creatinine was slightly elevated (1.27 mg/dL). Urinalysis showed 48 red blood cells/μL, 6 white blood cells/μL and elevated proteins (4.4 g/L; normal <0.2 g/L). The lipid profile on fasting serum showed a high triglyceride level contrasting with a low total cholesterol level (Table 1). Repeated blood smears and antigenic tests for malaria were negative as well as stool examination and all urine, stool, and blood cultures. On the day of admission (day 5 POS), a chest X-ray was normal and abdominal ultrasound showed a slight hepato-

Table 1 Evolution of the relevant laboratory parameters in the course of the hantavirus infection (POS denotes post-onset of symptoms)

Laboratory parameters (normal values)	Day 5 POS	Day 6 POS	Day 8 POS	Day 12 POS	Day 20 POS
Hemoglobin g/dL (12–15)	15.4	12.8	11.4	9.6	11.7
Leukocyte count /μL (3,500–9,000)	9,360	10,300	7,900	9,400	6,920
Platelet count /μL (150,000–450,000)	101,000	95,000	200,000	434,000	374,000
Creatinine mg/dL (0.6–1)	1.27	2.74	5.89	0.89	0.53
Urea mg/dL (15–37)	43	60	86	12	16
Kalium mEq/L (3.5–5)		5	3.7	3.3	
Natrium mEq/L (137–145)		122	127	141	
Alanine aminotransferase IU/L (9–52)	72	52	38	31	38
Aspartate aminotransferase IU/L (14–36)	115	72	39	38	44
Lactate dehydrogenase IU/L (313–618)	1,167	917	884	738	524
C-reactive protein mg/dL (<0.5)	10.5	8.6	5.0	1.0	<0.30
Total cholesterol mg/dL (<190)	98				240
Triglycerides mg/dL (<150)	442				682
Serology hantavirus ELISA IgM ratio (<0.9)	13.10				9.57
Serology hantavirus ELISA IgG (<0.9)	0.93				6.82
Polymerase chain reaction hantavirus (PUUV)	Positive				Negative

Interpretation of ELISA results: ratio <0.9: negative, 0.9–1.1: equivocal, >1.1: positive

megaly (140 mm), a borderline splenomegaly (127 mm), a normal right kidney (126×61 mm) and an enlarged left kidney (137×61 mm). The patient was immediately treated with intravenous ceftriaxone for suspected typhoid fever or leptospirosis. The fever abated rapidly, but over the following days she developed a quick deterioration of renal function, despite abundant intravenous rehydration. On day 8 POS, the creatinine level was 5.9 mg/dL (Table 1), the creatinine clearance 18 mL/min, and proteinuria 950 mg/24 h. Her blood pressure increased to a maximum

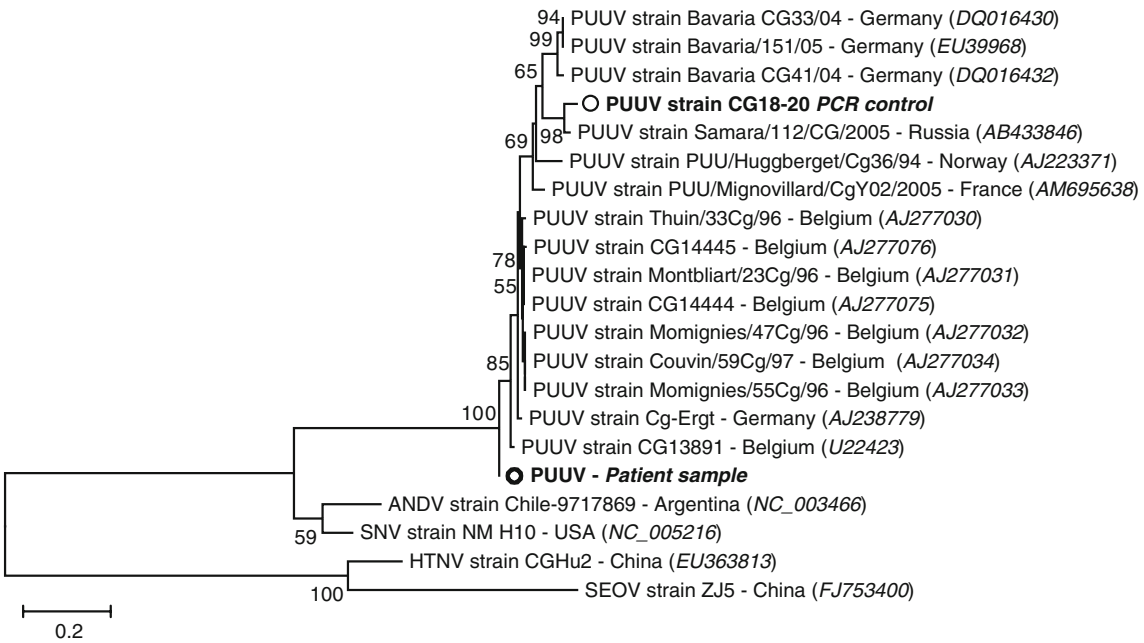

Fig. 1 Neighbor-joining phylogenetic tree of PUUV strains based on S segment partial sequences calculated using PAUP* software. The patient-associated sequence is marked by a *black circle*. The PCR control (*Puumala virus* strain CG 18–20) is marked by a *white circle*. Bootstrap values of ≥70%, calculated from 1,000 replicates, are shown at the tree branches. The scale bar indicates an evolutionary distance of 0.2 substitutions per position. *PUUV Puumala virus, ANDV Andes virus*, *HTNV Hantaan virus*, *SEOV Seoul virus*, *SNV Sin Nombre virus*

of 185/105 mmHg, requiring transient treatment with amlodipine. Oxygen saturation, however, remained normal. No hemodialysis was deemed necessary, since no clinical or radiological signs of fluid overload were observed, and because the kalemia remained subnormal (Table 1). The renal function rapidly improved spontaneously, with a normalization of the creatinine level and a disappearance of the proteinuria at day 12 POS.

Paired serology remained negative for *Leptospira* spp., dengue, *Coxiella burneti*, *Rickettsia conori*, and *R. mooseri*, *Brucella* spp. and *Entamoeba histolytica.* Serological testing by IgG and IgM ELISA (Focus Diagnostics, Cypress, CA, USA) on day 5 POS showed an IgM ratio of 13.10 (negative <0.90) and an IgG ratio of 0.93 (negative <0.90). In the convalescent phase (day 20 POS), IgM and IgG ratios were 9.57 and 6.82 respectively (Table 1). Reverse-transcriptase polymerase chain reaction (RT-PCR) was therefore performed on the initial serum and revealed a hantavirus serotype *Puumala* (PUUV) clustering phylogenetically with strains circulating in Belgium (Fig. 1).

Discussion

The diagnosis of acute hantavirus infection was rather straightforward in this backpacker returning from a journey in Ecuador, after common tropical infections had been excluded. The clinical picture was indeed suggestive of NE, and acute (and convalescent) screening with a commercial ELISA test confirmed this diagnosis, with highly positive (but diminishing) IgM values and a clear seroconversion for IgG. Moreover, serum lipids on the acute sample showed the typical "lipid paradox," as already noted in previous NE cases [3–5] and in American hantavirus cases (J.C., unpublished observations). This "lipid paradox" consists in the combination in the same fasting serum sample of a very low total (and HDL−) cholesterol, in contrast to a very high level of triglycerides. This (very transient) phenomenon is probably caused by the so-called cytokine storm, a now accepted key factor in all hantavirus syndromes [6]. Although admittedly low cholesterol levels are encountered in other severe infections, such as malaria and leptospirosis, the unusual combination with fasting hypertriglyceridemia seems rather specific to acute hantavirus infections, and in any case allows a quick first-step diagnostic approach. Moreover, hyponatremia and hypokalemia, despite serious acute renal failure, are other typical signs often encountered in NE [7].

Initially, Ecuador was the presumed country of infection because of the patient's likely heavy exposure to rodents and the compatible incubation period, typically 2 weeks (range from 5 to 42 days). However, PUUV, the etiological hantavirus of NE and its rodent reservoir, the bank vole (*Myodes glareolus*), are absent from the Americas. Exposure to the hantavirus in Belgium seemed very elusive since the patient was living exclusively in a city and did not mention any suspect out- or indoor activities upon return from Ecuador. We hypothesized, therefore, that an infection with SEOV might have occurred in Ecuador, although such an infection has never been reported so far in this country, to our knowledge. However, cases of SEOV-induced HFRS have been suggested in Brazil [2, 8] and demonstrated in the United States [9]. In fact, the very first clinical cases to be seroconfirmed as hantavirus infections in the Americas were Brazilian HFRS cases with heavy rat exposure, first considered to have leptospirosis [10]. Seoul viruses were even among the first hantaviruses to be isolated in both North and South America [11, 12]. Finally, since Focus Diagnostics ELISA testing does not permit pinpointing of the hantavirus serotype involved, we decided to forward the acute sample for molecular investigation, which turned out to be positive for PUUV. Moreover, after sequencing, the infecting PUUV fitted well into the Belgian clade of other known PUUV viruses (Fig. 1). Assessing once again the patient's history, it appeared that after her Ecuador trip, she passed a quiet week-end at her parents' cottage in Lille, a rural place situated in a lightly forested region, east of Antwerp, and known to be the most endemic area for PUUV in the North of Belgium. Indeed, Cg 13891, Cg 14444, and Cg 14445 (Fig. 1) had already been isolated in 1985 from bank voles captured in this area, thereby yielding the earliest European PUUV isolates outside of Scandinavia [13].

Conclusions

This case illustrates the increasingly challenging diagnostic dilemma in highly mobile travelers, and the benefit of RT-PCR in such cases, since this technique can not only confirm the clinical diagnosis in hantavirus infections, but may also allow geographical localization of the source of infection.

Conflict of interest None.

Financial support None

References

1. Hart CA, Bennett M (1999) Hantavirus infections: epidemiology and pathogenesis. Microbes Infect 14:1229–1237
2. Clement J, Neild GH, Maes P, Leirs H, Matthys P, Van Ranst M (2007) Symptomatic human hantavirus in the Americas. Emerg Infect Dis 2:345–346

3. Colson P, Damoiseaux P, Brisbois J, Duvivier E, Levecque P, Roger JM et al (1995) Epidémie d'hantavirose dans l'entre-Sambre-et-Meuse. Acta Clin Belg 50:197–205
4. Keyaerts E, Ghijsels E, Lemey P, Maes P, Zachee P, Daelemans R et al (2004) Plasma exchange-associated immunoglobulin m-negative hantavirus disease after a camping holiday in southern France. Clin Infect Dis 10:1350–1356
5. Hory B, Estavoyer JM, Cardot N, Couetdic G (1988) Serum lipids in muroid virus nephropathy. Nephron 48:166
6. Maes P, Clement J, Gavrilovskaya I, Van Ranst M (2004) Hantaviruses: immunology, treatment and prevention. Viral Immunol 17:481–497
7. Clement J, Maes P, Van Ranst M (2007) Acute kidney injury in emerging, non-tropical infections. Acta Clin Belg 62:387–395
8. Clement J, Neild G, Hinrichsen SL, Crescente JA, Van Ranst M (1999) Urban leptospirosis versus urban hantavirus infection in Brazil. Lancet 9194:2003–2004
9. Glass GE, Watson AJ, Leduc JW, Childs JE (1994) Domestic cases of hemorrhagic fever with renal syndrome in the United States. Nephron 1:48–51
10. Hinrichsen S, Medeiros de Andrade A, Clement J, Leirs H, McKenna P, Matthys P et al (1993) Evidence of Hantavirus infection in Brazilian patients from Recife with suspected Leptospirosis. Lancet 341:50
11. Leduc JW, Smith GA, Johnson KM (1984) Hantaan-like viruses from domestic rats captured in the United States. Am J Trop Med Hyg 5:992–998
12. Leduc JW, Smith GA, Pinheiro FP, Vasconcelos PF, Rosa ES, Maiztegui JI (1985) Isolation of a Hantaan-related virus from Brazilian rats and serologic evidence of its widespread distribution in South America. Am J Trop Med Hyg 4:810–815
13. Van der Groen G, Beelaert G, Hoofd G, Leirs H, Verhagen R, Yamanishi H et al (1987) Partial characterization of a Hantavirus isolated from a Clethrionomys glareolus captured in Belgium. Acta Virol 31:180–184